REMARKS

This responds to the Final Office Action mailed on October 16, 2009.

No claims have been amended, claims 1-172, 178, 195, 201, 204, 207-230 and 232-233 are canceled, and no claims have been added; as a result, claims 173-177, 179-194, 196-200, 202-203, 205-206, 231 and 234 are now pending in this application.

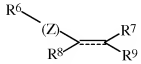
The Non-Statutory Obviousness-Type Double Patenting Rejections

Claims 173-177, 179-194, 196-200, 202-203, 205-206, 231, and 234 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 153-173 of copending application Serial No. 10/729,056. As neither the present application nor the ′056 application has been allowed, no terminal disclaimer is required at this time. Should a terminal disclaimer be required, the Office may request it upon a notice of allowable subject matter in either the present application or the ′056 application.

Claims 200, 202-203 and 205-206 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 8 of U.S. Patent No. 6,410,587 in view of Grainger et al. (WO 94/26303). This rejection is respectfully traversed.

In particular, the Examiner asserts that although the conflicting claims are not identical, they are not patentably distinct because the patent discloses and teaches an aspect of the claims in the present application in view of Grainger et al. (administration of the same active agent to the same subject) and that any mechanism of action of increasing the level of TGF-beta is obvious upon administration of the same active agent to the same subject.

Claim 8 in the ′587 patent is directed to a therapeutic method for lowering serum cholesterol comprising administering to a mammal in need of such therapy, an effective amount of a compound of formula VI:



(VI)

wherein

R^6 is (C_1-C_6)alkyl, or aryl, optionally substituted by 1, 2, or 3 V;

R^7 is phenyl, optionally substituted by 1, 2, or 3 V; or R^7 is (C_1-C_{12})alkyl, halo(C_1-C_{12})alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkylcyclo(C_1-C_6)alkyl, (C_3-C_6)cycloalkenyl, or (C_1-C_6)alkyl(C_3-C_6)cycloalkenyl;

R^8 is hydrogen or phenyl optionally substituted by 1, 2, or 3 V;

R^9 is heteroaryl, heteroaryl(C_1-C_3)alkyl, (C_1-C_4)alkoxycarbonyl(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkylcyclo(C_1-C_6)alkyl, (C_3-C_6)cycloalkenyl, or (C_1-C_6)alkyl(C_3-C_6)cycloalkenyl, wherein any aryl or heteroaryl may optionally be substituted by 1, 2, or 3, V;

----- is a single bond or is -C(B)(D)-, wherein B and D are each independently hydrogen, (C_1-C_6)alkyl, or halo;

V is OPO_3H_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, mercapto, (C_1-C_4)alkylthio, halo, trifluoromethyl, pentafluoroethyl, nitro, $N(R_n)(R_o)$, cyano, trifluoromethoxy, pentafluoroethoxy, benzoyl, hydroxy, $-(CH_2)_{0-4}C(=O)(C_1$-$C_6)$alkyl, $-UC(=O)(C_1$-$C_6)$alkyl, benzyl, $-OSO_2(CH_2)_{0-4}CH_3$, $-U(CH_2)_{1-4}COOR_p$, $-(CH_2)_{0-4}COOR_p$, $-U(CH_2)_{2-4}OR_p$, $-(CH_2)_{0-4}OR_p$, $-U(CH_2)_{1-4}C(=O)R_k$, $-(CH_2)_{0-4}C(=O)R_k$, $-U(CH_2)_{1-4}R_k$, $-(CH_2)_{0-4}R_k$, or $-U(CH_2)_{2-4}OC(=O)R_p$; wherein U is O, $N(R_m)$, or S;

Z is $-(CH_2)_{1-3}$-, -O-, $-OCH_2$-, $-CH_2O$-, -C(=O)O-, $-N(R_q)$-, C=O, or a covalent bond;

R_k is amino, optionally substituted with one or two (C_1-C_6)alkyl; or an N-heterocyclic ring optionally containing 1 or 2 additional $N(R_l)$, S, or nonperoxide O, wherein R_l is H (C_1-C_6)alkyl, phenyl, or benzyl;

R_n and R_o are independently hydrogen, (C_1-C_6)alkyl, phenyl, benzyl, or (C_1-C_6)alkanoyl; or R_n and R_o together with the nitrogen to which they are attached are a 3, 4, 5, or 6 membered heterocyclic ring;

R_p is H or (C_1-C_6)alkyl; and

R_m and R_q are independently hydrogen, (C_1-C_6)alkyl, phenyl, benzyl, or (C_1-C_6)alkanoyl;

the compound is MER25;

or a pharmaceutically acceptable salt thereof.

Claim 200 in the present application is directed to a method of increasing the level of TGF-beta in a human identified as being afflicted with a cardiovascular indication characterized by a decreased lumen vessel diameter, comprising selecting an agent that is structural analog of tamoxifen or a pharmaceutically acceptable salt thereof that directly or indirectly elevates the level of active TGF-beta1 in a human and administering to a human identified as being afflicted with a cardiovascular indication an effective amount of the agent

The Examiner is respectfully reminded that it is only the claims of an issued patent, not the entire disclosure, that may be employed in support of an obviousness-type double patenting rejection. M.P.E.P. § 804(II)(B)(1). Moreover, all aspects of the claims must be considered not just "an aspect" when evaluating obviousness-type double patenting.

The claims at issue differ by at least the population to be treated, the agents employed in the methods, and/or the outcome to be achieved. Further, the agents recited in claim 8 of the '587 patent do not necessarily elevate TGF-beta levels, e.g., active TGF-beta1 levels. In this regard, the Examiner is requested to consider that not all structural analogs of tamoxifen elevate TGF-beta (see the Rule 132 Declaration filed on August 12, 2009 in copending application Serial No. 10/729,056; copy enclosed herewith), and not all agents that elevate active TGF-beta elevate latent TGF-beta (see, e.g., the '587 patent).

Thus, withdrawal of the nonstatutory obviousness-type double patenting rejection over the '587 patent and Grainger et al. is respectfully requested.

Claims 173-177, 179-194, 196-200, 202-203, 205-206, 231, and 234 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 5,847,007 in view of Chander et al. (Cancer Res., 51:5851 (1991)). This rejection is respectfully traversed.

The Examiner asserts that although the conflicting claims are not identical, they are not patentably distinct because the patent discloses and teaches an aspect of the claims in the present application, and both sets of claims encompass administration of the same active agent to the same subject for the purpose of increasing TGF-beta levels.

The claims in the '007 patent are directed to a method for preventing atherosclerosis in a mammal at risk therefore, or treating atherosclerosis in a mammal, which method comprises orally administering to the mammal the following: a dose of a therapeutic agent in an amount effective when administered orally to elevate the level of TGF-beta, wherein the increase in TGF-beta inhibits atherosclerotic lesion formation or development in the mammal; and a therapeutic method comprising orally administering to a mammal an amount of a therapeutic agent effective upon oral administration to elevate the level of TGF-beta so as to treat a diseased blood vessel in said mammal, wherein said disease is associated with the diminution in the lumen volume of the diseased vessel, and wherein the therapeutic agent stabilizes atherosclerotic plaque, inhibits lipid accumulation, or inhibits or reduces diminution in vessel lumen diameter in the diseased vessel.

In contrast, claim 173 in the present application includes local administration of a cytostatic dose of a compound of formula (I) to a human; claim 182 in the present application includes administering a compound of formula (I) to a diabetic mammal; claim 200 in the present application includes selecting an agent that is structural analog of tamoxifen or a pharmaceutically acceptable salt thereof that directly or indirectly elevates the level of active TGF-beta1 in a human and administering an effective amount of that agent to a human; and claim 231 in the present application is directed to a method for treating arteriosclerosis, silent myocardial infarction, vascular insufficiency in the limbs, peripheral neuropathy, or retinopathy in a mammal with an effective amount of a compound of formula (I).

As discussed above, it is only the claims of an issued patent, not the entire disclosure, that may be employed in support of an obviousness-type double patenting rejection (see M.P.E.P. § 804(II)(B)(1)) and all aspects of the claims must be considered not just "an aspect" when evaluating obviousness-type double patenting. The claims at issue differ by at least the route of administration, population to be treated, the agents employed in the methods, and/or the outcome to be achieved. Further, the agents recited in claims 173 and 231 of the present application do

not necessarily elevate TGF-beta levels. In this regard, the Examiner is requested to consider that not all structural analogs of tamoxifen elevate TGF-beta (see the Rule 132 Declaration filed on August 12, 2009 in copending application Serial No. 10/729,056), and not all agents that elevate active TGF-beta elevate latent TGF-beta (see, e.g., the '587 patent, *supra*).

Therefore, withdrawal of the nonstatutory obviousness-type double patenting rejection over the '007 patent and Chander et al. is respectfully requested.

The 35 U.S.C. § 103 Rejections

Claims 173-175, 177, 179-181, 196-200, 203, 205-206, and 231 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Sawada et al. (Pharmacometrics, 44:357 (1992)). This rejection is respectfully traversed.

In the Response to Arguments section of the Office Action, the Examiner states that the Grainger Declaration has been carefully reviewed and considered, but is not persuasive. The Examiner points to Ito et al. (WO 94/09764) as teaching that toremifene is effective to treat blood vessel disease such as angitis.

However, there is nothing in the Office Action that responds to the following statements in the Declaration, which were provided to respond to the Office Action dated February 3, 2009: 1) all treated rodents in Sawada et al. and Ito et al. were female and that implies that toremifene was being used because of its anti-estrogenic property; 2) Sawada et al. do not provide a reasonable expectation that particular compounds that are structurally related to tamoxifen would have an activity that is not associated with the estrogen receptor but is associated with a therapeutic effect *in vivo* because it is not possible to determine the properties of the members of the recited class by understanding the properties of those compounds which also happen to be anti-estrogens and which exert particular properties as a result of that anti-estrogenic activity; 3) it was surprising that compounds within the scope of the claims would be useful to inhibit or treat a variety of cardiovascular or vascular indications, since the presence of anti-estrogenic activity in a sub-group of the compounds would not have predicted this; 4) as of the effective filing date of the present application, anti-estrogens would have been expected, if anything, to exacerbate the risk of cardiovascular disease, as estrogen was considered to be unequivocally cardioprotective, since (compared to men) women are relatively protected from cardiovascular

disease prior to menopause, when estrogen levels are higher, yet after the menopause have a similar age-corrected risk of cardiovascular disease to men; and 5) the lowering of total cholesterol by a particular agent does not by itself have any bearing on whether that the agent would in any way be beneficial in lowering "bad" cholesterol (that is, LDL cholesterol), much less indicate that the agent would be beneficial in preventing or inhibiting heart disease.

Thus, briefly, the Grainger Declaration evidences that as of Applicant's effective filing date, one of skill in the art in possession of Sawada et al. would not be motivated to employ toremifene to inhibit or treat a cardiovascular or vascular condition because any effect noted by Sawada et al. would be interpreted to be a result of the anti-estrogenic activity of toremifene, and anti-estrogens would have been expected to exacerbate the risk of cardiovascular disease. Dr. Grainger also states in the Rule 132 Declaration that it was surprising and unpredictable that compounds within the scope of the claims would be useful to inhibit or treat a variety of cardiovascular or vascular indications due to the presence of anti-estrogenic activity in a sub-group of the compounds.

In addition, the Grainger Declaration avers that the fact that toremifene lowered total cholesterol in female rats would not motivate one of skill in the art to use toremifene in a mammal suffering, for example, from atherosclerosis, because lowering total cholesterol does not by itself have any bearing on whether the same agent would in any way be beneficial in lowering LDL cholesterol, much less indicate that the agent would be beneficial in preventing or inhibiting heart disease.

The Examiner is respectfully reminded that all evidence in support of patentability must be considered and the Examiner must set forth the facts and reasoning that justify a conclusion that the proffered evidence is not sufficient (see M.P.E.P. § 2145). The Examiner has failed to provide those facts and reasoning and so issuing a final rejection is improper.

Accordingly, withdrawal of the finality of the rejection and proper consideration of the Rule 132 Declaration submitted with the response on August 3, 2009 are respectfully requested.

Thus, withdrawal of the § 103 rejection over Sawada et al. is respectfully requested.

Claims 173-177, 179-194, 196-199, and 205-206 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Yang (U.S. Patent No. 5,445,941). This rejection is respectfully traversed.

The Examiner asserts that because Yang teaches that toremifene is useful to treat osteoporosis in view of the correlation between osteoporosis and coronary artery disease, atherosclerosis and myocardial infarction and data that toremifene increased secretion of TGF-beta from human fetal fibroblasts in the absence of the estrogen receptor (ER), one of skill in the art would have been motivated to employ toremifene in a patient with osteoporosis regardless of the secondary conditions.

Yang do not teach the use of toremifene to treat osteoporosis. Moreover, even assuming for the sake of argument Yang provided data in support of the use of toremifene to treat osteoporosis, since osteoporosis is primarily associated with women over the age of 50, the "correlation" between osteoporosis and other diseases, the frequency of which increases with age, would not be a factor considered by one of skill in the art to be relevant to whether a drug useful to treat one disease would be useful to treat another. That is, one skilled in the art would not reasonably conclude that a drug useful to treat one disorder in a certain age group of people would be useful to treat a different disorder in that age group just based on a common age.

Further, the Examiner has failed to respond to Dr. Grainger's statements in the Rule 132 Declaration that the isoform of TGF-beta secreted from the human fetal fibroblasts in Yang was not known and that the observation that toremifene induces TGF-beta secretion from human fetal fibroblasts does not logically lead to the conclusion that toremifene is useful for treating osteoporosis because those cells are not present in individuals with osteoporosis.

The Examiner is respectfully reminded that all evidence in support of patentability must be considered and the Examiner must set forth the facts and reasoning that justify a conclusion that the proffered evidence is not sufficient (see M.P.E.P. § 2145). The Examiner has failed to provide those facts and reasoning and so issuing a final rejection is improper. Accordingly, withdrawal of the finality of the rejection and proper consideration of the Rule 132 Declaration submitted with the response on August 3, 2009 are respectfully requested.

Withdrawal of the § 103 rejection over Yang is respectfully requested.

Claims 173-177, 179-194, 196-200, 202-203, 205-206, 231, and 234 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Grainger et al. (WO 94/26303) in view of Chander et al. This rejection is respectfully traversed.

In the Response to Arguments section of the Office Action, the Examiner states that the Grainger Declaration has been carefully reviewed and considered but is found unpersuasive. The Examiner asserts that the patient, condition to be treated and the effect are the same, and that the instantly claimed mechanism of action (elevating TGF-beta) is unavoidably achieved by the earlier treatment of the same disorder by Grainger et al.

With respect to claim 173, Grainger et al. do not provide a cytostatic dose of a compound of formula (I), and so at least do not provide the same agents. With respect to claim 182, Grainger et al. do not provide treating a diabetic mammal or a compound of formula (I), and so at least do not provide the same agents or patient, and with respect to claim 231, Grainger et al. do not provide a compound of formula (I) or treating a condition selected from the group consisting of arteriosclerosis, silent myocardial infarction, vascular insufficiency in the limbs, peripheral neuropathy, and retinopathy, and so at least do not provide the same agents or condition to be treated. With respect to claim 200, Grainger et al. do not provide for selecting a structural analog of tamoxifen that elevates TGF-beta1 levels or its use, and so at least do not provide the same agents.

Chander et al., which disclose idoxifene, do not supply what is missing in Grainger et al.

As discussed above, the Grainger Declaration points out that it was surprising that compounds within the scope of the claims in the present application would be useful to inhibit or treat a variety of cardiovascular or vascular indications, as they would have been expected to act as anti-estrogens and that would have been expected to exacerbate the risk of cardiovascular disease. Moreover, although certain compounds may be structurally related to tamoxifen, not all of those compounds have a beneficial effect as a result of their TGF-beta, e.g., TGF-beta1, elevating property, which property is unrelated to anti-estrogenic activity (see the Rule 132 Declaration filed on August 12, 2009 in copending application Serial No. 10/729,056).

The Examiner is respectfully reminded that all evidence in support of patentability must be considered and the Examiner must set forth the facts and reasoning that justify a conclusion

that the proffered evidence is not sufficient (see M.P.E.P. § 2145). The Examiner has failed to provide those facts and reasoning and so issuing a final rejection is improper. Accordingly, withdrawal of the finality of the rejection and proper consideration of the Rule 132 Declaration submitted with the response on August 3, 2009 are respectfully requested.

Therefore, withdrawal of the § 103 rejection over Grainger et al. and Chander et al. is respectfully requested.

Claims 231 and 234 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Yang in view of Frank (Ophthalmology, 98:586 (1991)). This rejection is respectfully traversed.

Neither Yang nor Frank et al. teach the use of toremifene to treat arteriosclerosis, silent myocardial infarction, vascular insufficiency in the limbs, peripheral neuropathy, or retinopathy. Further, the Examiner has failed to respond to Dr. Grainger's statements in the Rule 132 Declaration that the isoform of TGF-beta secreted from the human fetal fibroblasts in Yang was not known and that the observation that toremifene induces TGF-beta secretion from human fetal fibroblasts does not logically lead to the conclusion that toremifene is useful for treating osteoporosis (or any other disorder) because those cells are not present in individuals with osteoporosis. Nor does Frank et al. supply the missing logic.

The Examiner is respectfully reminded that all evidence in support of patentability must be considered and the Examiner must set forth the facts and reasoning that justify a conclusion that the proffered evidence is not sufficient (see M.P.E.P. § 2145). The Examiner has failed to provide those facts and reasoning and so issuing a final rejection is improper. Accordingly, withdrawal of the finality of the rejection and proper consideration of the Rule 132 Declaration submitted with the response on August 3, 2009 are respectfully requested.

Hence, withdrawal of the § 103 rejection over Yang and Frank et al. is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402--0938
(612) 373-6959

Date February 12, 2010

By /Janet E. Embretson/
Janet E. Embretson
Reg. No. 39,665

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 12th day of February, 2010.

DAWN M. POOLE

Name

/ Dawn M. Poole /

Signature